Nicotine Effects on Presynaptic Receptor Interactions[a]

H. SERSHEN,[b,c] E. TOTH,[b] A. LAJTHA,[b] AND E. S. VIZI[d]

[b]*The N. S. Kline Institute for Psychiatric Research*
Center for Neurochemistry
Orangeburg, New York 10962

[d]*Institute of Experimental Medicine*
Hungarian Academy of Sciences
Budapest, Hungary

Presynaptic regulation of neurotransmitter release in the brain influences the amount of neurotransmitter released. This may or may not depend on nerve activity, and can be modulated by other factors that influence the membrane potential of the nerve ending. The neurotransmitter itself can inhibit its own release by acting on presynaptic autoreceptors. Other transmitters can also act presynaptically to modulate transmitter outflow. The complexity and diversity of such modulatory mechanisms of release have received much attention. We were particularly interested in receptor–receptor interactions influenced by participation of nicotine in the central actions of nicotine involving presynaptic effects.

The mechanisms of these receptor–receptor interactions have been discussed recently. In receptor heteroregulation, neurotransmitters or neuromodulators, by binding to receptors on the neuronal membrane, may be able to regulate the characteristics and function of the recognition sites of another transmitter or modulator receptor. Whereas autoreceptor mechanisms regulate the sensitivity of a receptor and are modulated by the levels of its ligand through positive or negative feedback loops, heteroreceptor mechanisms include direct or indirect interactions between different receptors and transmitters, involving the plasma membrane, intracytoplasmatic loops, or interactions at the nuclear level.[1]

The mechanism of action of nicotine could be elucidated by the understanding of these different receptor–receptor and receptor–transmitter interactions.

NICOTINIC-CHOLINERGIC-DOPAMINERGIC INTERACTIONS

Our interest in studying the effect of nicotine on cerebral neurotransmitter systems was stimulated by a number of studies reporting that the incidence of smoking is lower in patients with Parkinson's disease, and that the lower rate of smoking may predate neurological symptoms.[2] A number of possible explanations exist including, for example, that nicotine affects dopaminergic cells. While examining nicotine-induced rotation after nigral lesions,[3] we found a dopamine-like action of nicotine, which indicated enhancement of activity in the intact nigrostriatal system, without any sign of tolerance after repeated nicotine administration. The nicotine antagonist mecamylamine blocked the induced rotation. There was no

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[c]Corresponding author.

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evidence of a change in dopamine metabolism after an acute challenge with nicotine or of a sustained change after repeated injection, although a modification of dopaminergic response to nicotine could not be excluded. Stimulation of nigrostriatal dopamine neurons by nicotine had been shown previously.[4] The nucleus accumbens seems to be a major site of nicotine action in the brain. After chronic nicotine treatment (6 weeks), the K_d and the B_{max} for domperidone in the accumbens increased severalfold with no changes observed in the caudate putamen or the frontal cortex. Such effects may influence preparkinsonian persons in regard to smoking.[5] The fairly specific effects in the accumbens suggest that the dopamine receptors in this structure differ from those in other areas. Pharmacological differences between the nigrostriatal and mesolimbic dopaminergic systems have been observed before.[6] After an acute dose of nicotine, we observed increased dopamine turnover in the accumbens;[7] changes in a number of other areas examined were minor. These results further indicated that the accumbens is an important site of nicotine action. Although nicotine receptors were shown to be located on norepinephrine and serotonin terminals as well,[8] little effect of nicotine on these neurotransmitters was observed in the accumbens;[7] however, changes in the cerebral levels of catecholamines and serotonin were observed after acute or chronic nicotine administration.[9] At high levels *in vitro* nicotine inhibited vesicular dopamine uptake,[10] an effect that may not occur under conditions of tobacco smoking. Nicotine effects on vesicular function may play a part in the effects on transmitter release.

Inasmuch as acetylcholine release in the striatum is inhibited by endogenous dopamine, nicotinic effects on the cholinergic system may be modulated by dopaminergic-nicotine effects. We found evidence for the presence of nicotinic receptors on striatal cholinergic interneurons. Nicotine increased acetylcholine release in striatal slices only after dopaminergic lesions;[11] in the control animals the nicotine-induced increased dopamine release probably inhibited the stimulation of acetylcholine release, because the release of acetylcholine is tonically inhibited by the endogenous dopamine. These findings indicate the existence of nicotinic receptors on striatal cholinergic interneurons, probably on the somatodendritic part. With electrically stimulated striatal slices, the effect of nicotine in releasing dopamine involved the participation of N-type calcium channels;[12] nicotine receptor-operated ion channels permeable to calcium and N-type voltage-sensitive Ca^{2+} channels may act additively to increase intracellular free Ca^{2+} levels. Thus, nicotine effects include those on the level of intracellular calcium. Increases in intracellular calcium by nicotine in cortical neuronal cultures have been reported.[13]

EFFECTS OF CHRONIC NICOTINE ADMINISTRATION

Because smoking exposes the nervous system to nicotine intermittently over a long period of time, chronic nicotine effects are of special interest. The increase in K_d and B_{max} of dopaminergic binding after nicotine has already been mentioned.[5] Chronic nicotine was reported to have a protective effect on dopamine cells in the substantia nigra after partial hemitransection.[14] We found that after an MPTP lesion nicotine had no effect on the lesion or on the rate of terminal recovery, as measured by the rate of recovery of striatal dopamine. This finding confirmed the report that exposure to cigarette smoke does not decrease the toxicity of MPTP.[15,16] In testing ligand binding at dopamine D_1 and D_2 receptors, MPTP was shown to increase binding at the D_2 site, and nicotine to increase binding at the D_1 site. The two effects were independent: nicotine did not influence MPTP effects, and MPTP did not alter nicotine effects. The fact that nicotine alters the ratio of D_1 to D_2 receptor binding

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activities is of interest because such ratio changes may play a role in the therapeutic effects of neuroleptics.[17]

Nicotine was shown to increase dopamine release in striatal slices of both untreated and chronic nicotine-treated mice. Dopamine metabolism was not affected. The higher rate of efflux of dopamine in response to electrical stimulation in the striatum of nicotine-pretreated animals suggests that chronic nicotine may affect the mechanism of transmitter release in dopaminergic nerve terminals. Dopamine agonists inhibited and antagonists enhanced the release—effects that were abolished in chronic nicotine-treated animals. The findings were interpreted to mean that increased release of dopamine by nicotine leads to dopamine D_2 autoreceptor subsensitivity, with nicotine possibly attenuating autoinhibition of dopaminergic neurotransmission in the striatum.[18] Although it is generally accepted that nicotine increases dopamine release by stimulating specific receptors on striatal dopaminergic nerve terminals, the identification of the subcellular dopamine pools involved in its action is controversial. Presynaptic autoreceptors respond to increased dopamine release with a reduced sensitivity. As a result of this impaired autoregulation of transmitter release, electrical stimulation induces higher dopamine efflux from striatum exposed to repeated nicotine. Such changes also result in altered behavioral responses, as evidenced by an attenuation of apomorphine-induced hypomotility in chronic nicotine-treated mice.[19] The resulting decrease in autoreceptor stimulation after chronic nicotine would reduce the response of D_2-autoreceptor agonists to decrease dopamine release, showing that both acute and chronic nicotine administration can induce changes in the dopaminergic system.

NICOTINE EFFECTS ON OTHER RECEPTORS

When nicotine was administered intracerebrally in specific regions via microdialysis, the release of other neurotransmitters in addition to that of dopamine could be observed. Extracellular levels of serotonin increased in the cingulate and frontal cortex, and norepinephrine increased in the substantia nigra, cingulate cortex, and pontine nucleus.[20] The effect of nicotine on dopamine release was inhibited by cholinergic, dopaminergic, and also glutamatergic antagonists, indicating that glutamic acid release participates in nicotine-induced dopamine release.[20] The extracellular levels of some other amino acids such as glycine and taurine were also increased. The levels of some nonneurotransmitter amino acids were increased as well, indicating that cell permeability or amino acid transport processes are also affected by high local nicotine concentrations. Thus, cholinergic, catecholaminergic, glutamatergic, and membrane effects of nicotine could be shown.[21] The effects of nicotine in the brain are mediated by several receptor systems, and nonreceptor effects are also involved; nicotine effects show significant regional heterogeneity.

Neuropeptides may have a role in the complex effects of nicotine. A significant reduction of substance P was observed after a single dose of nicotine, primarily in areas in which nicotine acts; this effect may be mediated by dopamine-induced release of substance P. Nicotinic antagonists abolish this effect.[22] The rapid and large changes in the level of substance P caused by nicotine indicate a significant role for this peptide in nicotine effects in the brain.

HETEROGENEITY OF NICOTINIC RECEPTORS

One aspect of the complexity of the effect of nicotine in the nervous system is that it affects several neurotransmitter systems—some directly, through nicotinic sites on

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different cells, such as cholinergic, glutamatergic, etc. The released neurotransmitters such as glutamate may in turn modulate other transmitter systems, representing the indirect effects of nicotine.

An additional complexity is represented by the heterogeneity of the nicotinic binding sites. The regional heterogeneity of nicotine effects already indicates a heterogeneous distribution of nicotinic binding sites. The pharmacological heterogeneity of nicotinic sites is shown, for example, by the differences between the postsynaptic somatodendritic and neuromuscular sites.[23] It is possible that presynaptic and postsynaptic nicotinic sites also show differences, including different pharmacological properties. In turn, the pools of acetylcholine released by nicotine may come from several distinct transmitter pools or compartments.[24]

NICOTINE-INDUCED DOPAMINE AND NOREPINEPHRINE RELEASE

The effect of nicotine on dopamine release is well established and has been shown in the brain both *in vivo*[3,7,18] and *in vitro;* for example, in synaptosomal[25] and in brain slice[26] preparations. The effect of nicotine on norepinephrine release is less clearly established. Early studies examining nicotine effects on sympathetic axons in brain vessels[27] and in rat heart[28] did not find any release of norepinephrine; such release could be detected in peripheral nerve fibers.[29] In guinea-pig vas deferens nicotine enhanced resting and stimulation-evoked release of norepinephrine in acute but not in chronic experiments, thus indicating the presence of inhibitory muscarinic and facilitatory nicotinic receptors on noradrenergic axon terminals.[30] The findings suggest that nicotinic receptors located on noradrenergic axon terminals are different from those located postsynaptically in striated muscle or ganglia, but are similar to those at cholinergic axon terminals at the neuromuscular junction.

EFFECT OF NICOTINE ON GLUTAMATE RELEASE

Many of the striatal neurons of cortical origin are glutamatergic. When *in vivo* nicotine was infused via microdialysis into the striatum of rats, the level of glutamate in the dialysate increased more than fourfold, indicating a release of glutamate into the extracellular fluid.[20] Kynurenic acid, a glutamic acid receptor antagonist, inhibited this release. Kynurenic acid also inhibited the nicotine-induced release of dopamine in the striatum. The fact that kynurenic acid completely blocked the nicotine-induced dopamine release indicates that nicotine does not act directly on dopamine release, but indirectly through glutamate release. Indeed, nicotine significantly increases the extracellular levels of glutamate in a calcium-dependent manner, as measured with microdialysis in the striatum;[21] muscarinic antagonists blocked the effect. We interpreted this finding to mean that at least in part the dopamine-releasing activity of nicotine is mediated through its effect on the glutamatergic system.[20] Nicotine administered intracerebrally via microdialysis increased the extracellular levels of aspartic acid as well. Dopaminergic or nicotinic antagonists did not affect the changes in amino acid levels, but muscarinic antagonists were inhibitory. This finding indicates that muscarinic cholinergic receptors also participate in the action of nicotine in the nervous system.

The interaction between glutamatergic and dopamine neurons is also reciprocal; in particular, dopamine receptors are located on striatal afferent fibers of cortical origin and dopamine agonists can inhibit the release of glutamate.[31] Such interactions would be regionally heterogeneous.

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Adding to the complexity of the regulation of dopamine release, the presence of glutamate receptors on nondopamine neurons has been reported.[32] The nondopamine neurons mediating the effect of glutamate could be GABAergic interneurons. Glutamate appears to exert an inhibitory presynaptic control on dopamine release, indirectly mediated in part by GABAergic neurons, whereas glutamatergic neurons seem to have a facilitatory presynaptic influence on dopamine release. Thus, corticostriatal glutamatergic fibers have direct stimulatory and indirect inhibitory presynaptic effects on dopamine release.[32] A scheme of these receptor–receptor actions is given in FIGURE 1.

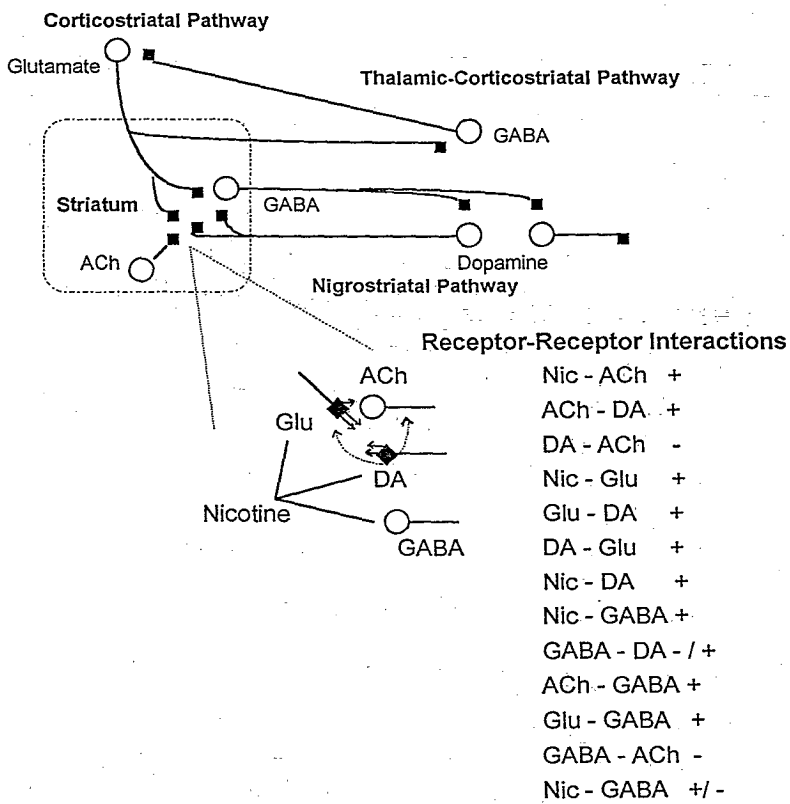

FIGURE 1. Schematic representation of nicotine-glutamatergic-dopaminergic presynaptic interactions.

INTERACTION OF RECEPTORS AT THE NUCLEAR LEVEL

Although not in the scope of this paper, interactions between receptors can also occur at the nuclear level because activation of one receptor coupled to adenylate cyclase can activate protein kinases, which in turn control the transcriptional activity

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of the gene for another receptor.[1] Nicotine may have direct effects on intracellular events involved in protein metabolism,[33] selectively affecting the metabolism of specific proteins only. The levels of some proteins were increased and others decreased. Thus, synthesis and breakdown are selectively affected. This reaction may involve effects at nuclear levels. Similar nuclear effects of nicotine are represented by the stimulation by nicotine of the expression of c-fos nuclear proteins, as early markers of neuronal activation.[34]

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